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10/527,275	03/09/2005	Josef Georg Heuer	X-15747	3793

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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

NOTIFICATION DATE	DELIVERY MODE
05/17/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,275	HEUER ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/9/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: Notice to Comply

DETAILED ACTION

Advisory Information

This application contains a sequence disclosure(s) that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132. Applicants are given the statutory time from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicants are requested to return a copy of the attached Notice to Comply with the reply.

In particular, there is an FGF-19 amino acid sequence (consisting of 216 amino acids) presented in the specification at pg 7, between lines 5-15. As stated in 37 CFR 1.821(c), "[p]atent applications which contain disclosures of nucleotide and /or amino acid sequences must contain, as a separate part of the disclosure, a paper copy disclosing the nucleotide and /or amino acid sequences and associated information using the symbols and format in accordance with the requirements of §§ 1.822 and 1.823. This paper copy is hereinafter referred to as the "Sequence Listing". Each sequence disclosed must appear separately in the "Sequence Listing". Each sequence set forth in the "Sequence Listing" shall be assigned a separate sequence identifier."

Therefore, Applicants need to provide a computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences recited in the claims and specification of the instant application which are encompassed by these rules; a paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence.

Status of Application, Amendments and/or Claims

The preliminary amendment of 3/9/05 has been entered in full. Claims 1-11 are canceled. New claims 12-20 are added.

Claims 12-20 are under consideration in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the mortality in patients with sepsis which comprises administering to the patients an effective amount of FGF-19 with the sequence as presented on page 7 of the specification, does not reasonably provide enablement for a method of (1) reducing the mortality of "critically ill patients"; (2) reducing the morbidity of sepsis or any other critically ill patient; or (3) reducing the mortality in patients with sepsis which comprises administering to the patients an effective amount of any FGF-10 with a sequence different from the sequence as presented on page 7 of the specification. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method of "reducing the mortality and morbidity in critically ill patients" comprising administering FGF-19. Independent claim 12 encompasses treatment of any critically ill patient. The specification does not provide a definition of the term "critically ill". However, the specification and claims envision that the term encompasses "systemic inflammatory response syndrome" (as recited in claim 13); "respiratory distress" (claim 14); "acute lung injury" (claim 15); "acute respiratory distress syndrome" (claim 16); "multiple organ dysfunction syndrome" (claim 17); "sepsis" (claim 18); as well as "noninfectious pathologic causes such as pancreatitis, ischemia, multiple trauma and tissue injury, hemorrhagic shock and immune-mediated organ injury" (pg 1, lines 13-16). Claims 12-18 each encompass any form of administration of FGF-19, while claims 19 and 20 each limit the administration to continuous infusion (claim 19) or bolus injection (claim 20). Each claim encompasses administration of "FGF-19"; the specification teaches that the "FGF-19 useful in the methods of the present invention includes human FGF-19, FGF-19 analogs, FGF-19 derivatives, and other agonists of the FGF-19 receptor" (pg 7; lines 30-32).

The specification provides the following working examples in support of the claimed invention. Example 1 describes administration of FGF-19 to an "in vivo model of sepsis" created by "cecal ligation and puncture" in "normal Balb/c mice" and reports that "81% of the mice treated with human serum albumin died while 56% of the mice treated with FGF-19 survived (p-value = .0683)" (pg 11). Example 2 describes administration of FGF-19 to female ob/ob mice and reports that the "FGF-19 lowered blood glucose in a dose dependent manner as soon as 1 hour post administration" (pg 11). The specific level of the lowered blood glucose is not disclosed. Example 3 describes "glucose uptake in 3T3-1 adipocytes" and reports "FGF-19 stimulated glucose uptake in 3T3-L1 adipocytes in a concentration dependent manner" (pg 11-12). Example 4 describes "transcriptional profiling of FGF-19 treated 3T3-L1 adipocytes" and reports that "[g]enes upregulated by FGF-19 treatment of 3T3-L1 adipocytes are chop-10, which is normally upregulated during nutritional stress and Fra-1 which has been associated with the regulation of glucose uptake" (pg 12).

The relevant art teaches that the "cecal ligation and puncture" model is a "widely used and carefully characterized model of infection that responds to fluid resuscitation and antibiotics, similar to human patients with sepsis" (pg 9 of Remick et al. 2005. Shock. 24(1): 7-11). The relevant art also teaches that, "[t]he CLP model is one of the most widely used models of sepsis and septic shock. It satisfies many of the criteria set out by critics listing essential attributes for an appropriate model: it is polymicrobial, has focal infection origins, produces septicemia, and releases bacterial products into the periphery" (pg 56 of Hubbard et al. 2005. Shock. 24(1): 52-57). In view of the working examples in the specification and the teachings of the relevant art, the specification provides enablement for a method of reducing the mortality in patients with sepsis which comprises administering to the patients an effective amount of FGF-19 with the sequence as presented on page 7 of the specification. However, the specification does not provide enablement for the following embodiments encompassed by the claims:

(1) Reducing the mortality and morbidity of "critically ill patients". Claims 12, 19 and 20 each encompass a method of reducing the mortality (rate of death) and morbidity (rate of incidence) of any type of critically ill patient by administration of FGF-19. Claims 13-17 limit the critically ill patients to ones with "systemic inflammatory response syndrome" (SIRS, claim 13); "respiratory distress" (RD, claim 14); "acute lung injury" (ALI, claim 15); "acute respiratory distress syndrome" (ARDS, claim 16); or "multiple organ dysfunction syndrome" (MODS, claim 17).

The specification does not provide a limiting definition of the term "critically ill" or teach how to distinguish patients that are "critically ill" from those that are merely "ill". The specification implies that "critically ill patients" include those with SIRS associated with sepsis as well noninfectious pathologic causes (pg 1). The specification further teaches that SIRS "as used herein describes an inflammatory process associated with a large number of clinical manifestations" (pg 3); that "sepsis" as used in the specification is "defined as SIRS arising from infection" (pg 4); and that "noninfectious pathogenic causes of SIRS may include pancreatitis, ischemia, multiple trauma and tissue injury i.e. crushing injuries or severe burns, hemorrhagic shock, immune-mediate organ injury, and the exogenous administration of such putative mediators of the inflammatory

process as tumor necrosis factor and other cytokines" (pg 4). The Examples of SIRS on page 2 also includes ARDS, shock, renal failure and MODS. The term "respiratory distress" is taught to include conditions wherein patients have difficulty breathing due to direct lung injury or due to a systemic process (pg 4).

In view of conditions recited in the claims, and the teachings of the specification, it is clear that the specification envisions treatment of a wide-range of conditions, both infectious and non-infectious, by administration of FGF-19. In support of the ability of FGF-19 to reduced the mortality or morbidity of these conditions, the specification provides a single working example of the reduction of mortality associated with sepsis. The relevant art teaches that acute lung injury (ALI) is "not a disease in and of itself, but rather it is a complication of either a direct or indirect injury to the lung"; "may result from a variety of acute diseases including sepsis, trauma, pneumonia, pancreatitis and hypertransfusion"; and "very little success has been achieved with regard to new treatment modalities. The spate of previous trial failures may relate to participant heterogeneity or to ambiguous pathophysiological rationale (i.e., anti-inflammatory strategies when inflammation is either not central or only a single component of the pathogenesis of the syndrome) among other reasons" (pg 633-634 of Esper et al. 2005. Expert Opin Investig Drugs. 14(5): 633-645). Esper also teaches that acute respiratory distress syndrome (ARS) is "almost synonymous" with ALI (pg 633).

In view of the teachings of the relevant post-filing art, and the limited nature of the teachings and working examples of the specification, the skilled artisan could not predict whether or not administration of FGF-19 would treat non-septic "critically ill" patients, such as those with SIRS, RD, ALI, ARDS or MODS that is not associated with sepsis. It would require undue experimentation for the skilled artisan to test whether or not FGF-19 could be used to treat the vast number of heterogeneous conditions encompassed by the claims.

(2) Claims 12-20 each encompass methods of reducing the "morbidity" of critically ill patients. "Morbidity" refers to the rate of incidence of a condition or disease. As set forth in the section, "Claim Rejections - 35 U.S.C. 112, 2nd Paragraph", the claims are indefinite with respect to reducing morbidity because the claims recite that

the patients to be treated already have a condition or disease; e.g., with respect to claim 18, how do you reduce the rate of incidence of sepsis in a patient that already has sepsis. However, for purposes of prosecution, the claim has been interpreted broadly to encompass methods of reducing the rate of occurrence (morbidity) of critical illnesses in patients that are not already critically ill. This includes reducing the rate of occurrence (morbidity) of SIRS, RD, ALI, RDS, MODS or sepsis in a patient that is "critically ill" but does not yet have one of said conditions. However, in view of the teachings of the relevant post-filing art, and the limited nature of the teachings and working examples of the specification, the skilled artisan could not predict whether or not administration of FGF-19 would reduce the rate of occurrence of critical illness in a non-critically ill patient, or SIRS, RD, ALI, RDS, MODS or sepsis in a critically ill patient. It would require undue experimentation for the skilled artisan to test whether or not FGF-19 could be used to reduce the rate of occurrence of the vast number of heterogeneous conditions encompassed by the claims. Even with respect to sepsis, the working example only provides support for reducing the rate of mortality in septic rodents. The working example does not provide any evidence that the rate of occurrence of sepsis was reduced in the experimental model of sepsis.

(3) Each of claims 12-20 encompasses a method comprising administration of "FGF-19", which is taught by the specification as encompassing "human FGF-19, FGF-19 analogs, FGF-19 derivatives, and other agonists of the FGF-19 receptor, hereinafter collectively known as FGF-19 compounds" (pg 7, lines 30-32). This genus is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the administered "FGF-19" possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims do not even limit the administered "FGF-19" to a polypeptide sequence. Thus, the claims are drawn to a genus of methods using FGF-19 polypeptides, analogs, derivatives and other agonists of the FGF-19 receptor (which is apparently not disclosed). Furthermore, the relevant art recognizes that "compound" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic,

transformed cells, radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.

Even with respect to FGF-19 polypeptides alone, the claims each encompass innumerable protein variants in which one or more amino acid residues are added, deleted or substituted in the 216 amino acid sequence presented on page 7. However, Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure or function between the protein corresponding to the disclosed sequence and variants of said protein. If a variant of the disclosed FGF-19 protein sequence is to have a structure and function similar to the disclosed parent protein, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue

experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

The specification suggests that FGF-19 compounds can be tested for the ability to work in the claimed methods by "an *in vivo* survival study" which is "described in Example 1" (pg 8, lines 6-7). However, due to the large quantity of experimentation necessary to generate the vast number of potential "FGF-19" compounds envisioned by the specification and encompassed by the term "FGF-19" in the claims, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the

breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claims 11-20 are genus claims because the claims are directed to methods of treatment using "FGF-19", which as taught by the specification encompasses "human FGF-19, FGF-19 analogs, FGF-19 derivatives, and other agonists of the FGF-19 receptor, hereinafter collectively known as FGF-19 compounds" (pg 7, lines 30-32). This genus is highly variant because a significant number of structural differences between genus members are permitted. The claims do not require that the administered "FGF-19" possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims do not even limit the administered "FGF-19" to a polypeptide sequence. Thus, the claims are drawn to a genus of methods using FGF-19 polypeptides, analogs, derivatives and other agonists of the FGF-19 receptor (which is apparently not disclosed). From the specification, it is clear that Applicants have possession of a method of reducing the mortality in patients with sepsis by administration of a FGF-19 polypeptide with the sequence disclosed on page 7, lines 5-14 (no sequence identifier has been provided).The specification fails to describe or teach any other "FGF-19" which lacks this sequence and can be used to treat sepsis or a critically ill patient.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of "FGF-19" to be used in the claimed methods or cells. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish compounds that are "FGF-19" from other compounds are missing from the disclosure. The specification and claims do not provide any description of what changes should be made to the disclosed sequence on page 7. There is no description of the sites in this sequence at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the "FGF-19" compounds encompassed. Thus, no identifying characteristics or properties of the instant "FGF-19" compounds are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a method comprising administration of an FGF-19 polypeptide with the sequence disclosed on page 7, lines 5-15, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "critically" in claim 1 is a relative term which renders the claim indefinite. The term "critically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "ill" is rendered

indefinite by use of the term "critically". It is unclear how to distinguish an illness that is "critical" from an illness that is "non-critical".

Claim 1 is also indefinite because it recites "reducing the mortality and morbidity in critically ill patients". The term "morbidity" refers to the rate of incidence of a disease or condition. In the claimed method the patient to be treated is "critically ill". As such it is unclear how a reduction in the "rate of incidence" of becoming critically ill can be effected if the patient is already "critically ill". For purposes of prosecution, the claim has been interpreted broadly to encompass methods of reducing the rate of occurrence (morbidity) of critically illnesses in patients that are not already critically ill.

The remaining claims are rejected for depending from an indefinite claim.

Art of Note

No prior art was identified that anticipates or suggests the methods encompassed by claims 12-20.

The following article was found by the Examiner during the art search while not relied upon for a rejection are considered pertinent to the instant application:

Fu et al, 2004. Endocrinology. 145(6): 2594-2603. Fu reports that "recombinant FGF19 increased metabolic rate, reduced body weight, and reversed the diabetes in both high-fat-fed mice and leptin-deficient mice" (pg 2595). It is noted that Fu was published in 2004 and the instant application claims priority to 8/18/2002.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

zch

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER